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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Etex Corporation
Application No. PCT/US97/18631
Filed: October 16, 1997
For: METHOD OF PREPARING A POORLY CRYSTALLINE CALCIUM PHOSPHATE AND METHODS OF ITS USE

ASSISTANT COMMISSIONER OF PATENTS
WASHINGTON, D.C. 20231

Sir:

RESPONSE TO WRITTEN OPINION

In response to the Written Opinion mailed September 22, 1998, Applicant submits Substitute Sheets no. 102-117 to replace sheets no. 102-114 originally filed with the application. The claims have been renumbered in the substitute sheets. For the convenience of the Examiner, changes are noted herein below, with additions indicated by underlining and deletions by brackets.

In the claims.

1. A self-hardening bioceramic composition, comprising:

[a hydrated precursor of] a calcium phosphate and an aqueous-based liquid in an amount sufficient to hydrate the calcium phosphate to form a paste or putty, [characterized in that] wherein the said paste or putty hardens and the hardening [of the hydrated precursor] is associated with an endothermic reaction.

2. [A] The self-hardening bioceramic composition, [comprising:] of claim 1, [a hydrated precursor of an amorphous calcium phosphate and an aqueous-based liquid in an amount sufficient to hydrate the calcium phosphate to form a paste or putty, characterized in that hardening of the hydrated precursor occurs in more than ten minutes] wherein the said paste or putty remains injectable or formable for a time greater than about 30 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

3. The composition of claim 2, wherein hardening occurs in more than 30 minutes.

4. The composition of claim 1, wherein the aqueous-based fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

5. The composition of claim 1 or 2, wherein the calcium phosphate comprises an amorphous calcium phosphate.

6. The composition of claim 1 or 2, wherein the calcium phosphate comprises a nanocrystalline calcium phosphate. [further comprising a promoter, said promoter capable of promoting the hardening of the hydrated precursor.]

7. The composition of claim 1 or 2, wherein the hardening of the hydrated precursor is further associated with the conversion of the calcium phosphate into a poorly crystalline apatitic calcium phosphate.

8. The composition of claim 7, further comprising a promoter, said promoter further capable of promoting the conversion of calcium phosphate into a poorly crystalline apatitic calcium phosphate.

9. The composition of claim [6 or] 8, wherein the promoter is selected from the group consisting of passive promoters and participant promoters.

10. The composition of claim 9, wherein the promoter is a passive promoter selected from the group consisting of metals, metal oxides, ceramics, silicates, sugars, salts, and polymeric particulates

11. The composition of claim 9, wherein the promoter is a passive promoter and said passive promoter is present in the range of about 1:1 to about 5:1 calcium phosphate:promoter.

12. The composition of claim 9, wherein the promoter is a passive promoter selected from the group consisting of SiO_2, mica, Al_2O_3, poly(L-lactide) (PLLA), polyglycolide (PGA), and poly(lactide-co-glycolide (PLGA) copolymers.

13. The composition of claim 9, wherein the promoter is a participant promoter selected from the group consisting of calcium and phosphorus sources.

14. The composition of claim 9, wherein the promoter is a participant promoter selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline hydroxyapatite, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

15. The composition of claim 9, wherein the promoter comprises DCPD.

16. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size less than about 200μm.

17. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size of less than about 95μm.

18. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size of about 35 - 45μm and a grain size maximum of less than about 110 μm.

[19. The composition of claim 1, further characterized in that hardening occurs in less than one hour at about 37 °C.]

20. The composition of claim 1 or 2, further characterized in that hardening occurs in more than 24 hours at about 4 °C.

21. The composition of claim 1, wherein the amount of liquid is in the range of

about 0.5 to about 2.0 ml. liquid g calcium phosphate.

22. A bioceramic composition, comprising:

a poorly crystalline calcium phosphate prepared by:

promoting the hardening of a hydrated precursor comprising an amorphous calcium phosphate and an aqueous-based liquid in an amount sufficient to hydrate the amorphous calcium phosphate to form a paste or putty.

whereby hardening is associated with an endothermic reaction and the conversion of the amorphous calcium phosphate into the poorly crystalline calcium phosphate.

23. A bioceramic composition, comprising:

a strongly bioresorbable, poorly crystalline apatitic calcium phosphate.

24. The composition of claim 22 or 23, wherein said poorly crystalline apatitic calcium phosphate has an X-ray diffraction substantially as shown in Figure [18] 7.

25. The composition of claim 23, wherein the strongly resorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

26. The composition of claim 23, wherein the X-ray diffractions pattern is characterized by an absence of peaks associated with the 210 Miller Index.

27. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one year when 1 g of the composite is placed in a rat intramuscular site.

28. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of

the poorly crystalline apatitic calcium phosphate is resorbed within nine months when 1 g of the composite is placed in a rat intramuscular site.

29. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within six months when 1 g of the composite is placed in a rat intramuscular site.

30. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within three months when 1 g of the composite is placed in a rat intramuscular site.

31. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one month when 1 g of the composite is placed in a rat intramuscular site.

32. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is formulated so that when implanted *in vivo* in a bone site, new bone substantially replaces the composite within six months.

33. The composition of claim 23, wherein the poorly crystalline apatitic calcium phosphate is formulated so that when implanted *in vivo* in a bone site, new bone substantially replaces the composite within six weeks.

107. The composition of claim 23, wherein powders of the poorly crystalline apatitic calcium phosphate are pressed into a powder compact of a predetermined shape.

34. A method of preparing a bioceramic composition, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a promoter, and

(c) an aqueous-based liquid in an amount sufficient to form a paste or putty,

whereby the paste or putty is converted into a poorly crystalline apatitic calcium phosphate and said conversion is associated with hardening of the paste in an endothermic reaction.

35. The method of claim 34, wherein the promoter is selected from the group consisting of SiO_2, Al_2O_3, sand, mica and glass.

36. The method of claim 34, wherein the promoter is a calcium or a phosphorus source.

37. The method of claim [34] 36, wherein the calcium or phosphate source is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline hydroxyapatite, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

38. The method of claim 34, wherein the [reaction is carried out at no greater than about 37 °C] paste or putty is injectable and formable for a time greater than about 10 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

39. The method of claim 34, wherein the fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

108. A method of preparing a bioceramic composition, comprising:

mixing powders of an amorphous calcium phosphate and a promoter; and

pressing the powders to form a powder compact of a predetermined shape.

109. The method of claim 108, further comprising hydrating the powder compact to promote conversion of the mixed powders to a poorly crystalline apatitic calcium phosphate.

110. The method of claim 108, wherein the fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

111. A bioceramic composition, comprising:

powders of an amorphous calcium phosphate and a promoter compressed to form a powder compact of a predetermined shape.

40. A composite material comprising:

(a) a poorly crystalline apatitic calcium phosphate made by the process comprising:

providing an amorphous calcium phosphate in the presence of a sufficient quantity of water to produce a paste; and

promoting the hardening of the paste, wherein said hardening is associated with an endothermic reaction and the conversion of the amorphous calcium phosphate to a poorly crystalline apatitic calcium phosphate; and

(b) a supplemental material in intimate contact with the poorly crystalline apatitic calcium phosphate, said supplemental material present in an amount effective to impart a selected characteristic to the composite.

41. [The material of claim 40] A composite material comprising:

(a) a poorly crystalline apatitic calcium phosphate made by the process comprising:

providing an amorphous calcium phosphate in the presence of a sufficient quantity of water to produce a paste; and

promoting the hardening of the paste, characterized in that, said paste, when prepared from a reaction of amorphous calcium phosphate and a second phosphate in a fluid, [the reaction mixture] is injectable [and] or formable for a time greater than about

10 minutes at about 22 [25]°C, and hardens within about 10 to 60 minutes at about 37 °C; and

(b) a supplemental material in intimate contact with the poorly crystalline apatitic calcium phosphate, said supplemental material present in an amount effective to impart a selected characteristic to the composite..

42. A composite material, comprising:

a strongly bioresorbable, poorly crystalline apatitic calcium phosphate in intimate contact with a biocompatible supplemental material, said supplemental material present in an amount effective to impart a selected characteristic to the composite.

43. The composite of claim 42, wherein said poorly crystalline apatitic calcium phosphate has x-ray diffraction substantially as shown in Figure [18] 7.

44. The composite of claim 42, wherein the strongly resorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

45. The composite of claim 42, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one year when 1 g of the composite is placed in a rat intramuscular site

46. The composite of claim 42, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate,] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within nine months when 1 g of the composite is placed in a rat intramuscular site

47. The composite of claim 42, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly

crystalline apatitic calcium phosphate.] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within six months when 1 g of the composite is placed in a rat intramuscular site

48. The composite of claim 42, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate.] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within three months when 1 g of the composite is placed in a rat intramuscular site

49. The composite of claim 42, wherein the poorly crystalline apatitic calcium phosphate is [formulated so that when the composite compromises at least 1 g of poorly crystalline apatitic calcium phosphate.] characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one month when 1 g of the composite is placed in a rat intramuscular site

50. The composite of claim 42, wherein the supplementary material is bioresorbable.

51. The composite of claim 50, wherein the resorbable supplementary material is selected from the group consisting of collagen, demineralized bone matrix, derivativized hyaluronic acid, polyanhydrides, polyorthoesters, polyglycolic acid, alginate, polylactic acid, and copolymers thereof, polyesters of α-hydroxycarboxylic acids, poly(L-lactide) (PLLA), poly(D,L-lactide) (PDLLA), polyglycolide (PGA), poly(lactide-co-glycolide (PLGA), poly(D,L-lactide-co-trimethylene carbonate), and polyhydroxybutyrate (PHB), polyanhydrides, poly(anhydride-co-imide) and co-polymers thereof, and bioactive glass compositions.

52. The composite of claim 42, wherein supplementary material is non-bioresorbable.

53. The composite of claim 52, wherein the non-bioresorbable supplementary

material is selected from the group consisting of dextrans, polyethylene, polymethylmethacrylate (PMMA), carbon fibers, polyvinyl alcohol (PVA), polyethylene terephthalate/polyamide, bioglasses, calcium sulfate and calcium phosphates

54. The composite of claim 42, wherein the supplementary material is a lubricant.

55. The composite of claim 54, wherein the lubricant is selected from the group consisting of silicone oil, polymer waxes, lipids, surfactants and fatty acids.

90. The composite material of claim 54, wherein the lubricant in present in an amount in the range of about 0.1-30 wt%.

91. The composite material of claim 42, wherein the supplementary material comprises a radiographic material.

56. The composite of claim 42, wherein the supplementary material is in the form selected from the group consisting of foam, sponge, mesh, particles, fibers, gels and filaments.

92. The composite material of claim 42, wherein the supplementary material is in the form of a fiber and the fiber is present in an amount in the range of about 0.01-50 wt%.

57. A method of preparing a ceramic composite material, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a promoter, and

(c) a supplementary material, the supplementary material present in an amount effective to impart a selected characteristic to the composite; and

initiating conversion of the amorphous calcium phosphate into a poorly crystalline apatitic calcium phosphate, said conversion is associated with an endothermic reaction

[hardening at about 37 °C of the composite within 10 to 60 minutes].

58. The method of claim 57, wherein the promoter is selected from the group consisting of Al_2O_3, sand, mica and glass.

59. The method of claim 57, wherein the promoter is a calcium or a phosphorus source.

60. The method of claim 59, wherein the promoter is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline HA, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

61. [The method of claim 57,] A method of preparing a ceramic composite material, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a promoter, and

(c) a supplementary material, the supplementary material present in an amount effective to impart a selected characteristic to the composite; and

initiating conversion of the amorphous calcium phosphate into a poorly crystalline apatitic calcium phosphate, wherein the reaction [is carried out at no greater than about 37 °C] mixture is injectable or formable for a time greater than about 10 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

62. The method of claim 57, wherein the reaction to form a poorly crystalline apatitic calcium phosphate is initiated before addition of the supplementary material.

63. The method of claim 57, wherein the reaction to form a poorly crystalline apatitic calcium phosphate is initiated after addition of the supplementary material.

64. The method of claim 57, wherein the reaction is initiated by addition of a fluid, the fluid selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

65. An orthopedic device comprising the composite of claim 42.

66. A bone cement comprising the composite of claim 42.

93. The orthopedic device of claim 65, wherein the device is selected from the group consisting of pins, nails, screws, plates and anchors.

94. The orthopedic device of claim 65, wherein the supplementary material is in the form of particulants or fibers.

95. The orthopedic device of claim 94, wherein the supplementary material is present in an amount in the range of about 1-20 wt%.

96. The bone cement of claim 66, wherein the supplementary material is selected to increase compressibility or lead bearing properties of the cement.

97 The bone cement of claim 66, wherein the supplementary material comprises fibers.

98. The bone cement of claim 66, wherein the supplementary material comprises a binder.

67. A method for embedding an object at a bone site, comprising:

preparing a composite comprising a fully resorbable, poorly crystalline apatitic calcium phosphate in intimate contact with a non-resorbable or weakly resorbable supplementary material;

introducing the composite to a bone site, whereby the fully resorbable poorly crystalline apatitic calcium phosphate is resorbed and ossified and the non-resorbable

supplementary material remains at the bone site.

68. A method for treating a bone defect, comprising:

identifying a bone site suitable for receiving an implant; and

introducing a strongly resorbable, poorly crystalline apatitic calcium phosphate at the implant site, whereby bone is formed at the implant site.

69. A method for treating a bone defect, comprising:

identifying a bone site suitable for receiving an implant; and

introducing a hydrated precursor to a strongly resorbable, poorly crystalline apatitic calcium phosphate at the implant site, whereby the hydrated precursor is converted *in vivo* to a poorly crystalline apatitic calcium phosphate and whereby bone is formed at the implant site.

99. The method of claim 67, wherein the poorly crystalline apatitic calcium phosphate is introduced in the form selected from the group consisting of paste, putty and preshaped object.

70. The method of claim 68, wherein the poorly crystalline apatitic calcium phosphate is introduced in the form selected from the group consisting of paste, putty and preshaped object.

71. The method of claim 69, wherein the hydrated precursor is introduced in the form selected from the group consisting of paste and putty.

72. The method of claim 99, 70 or 71, characterized in that, said paste is injectable for a time greater than about 10 minutes at about 22 [25]°C, hardens within about 10 to 60 minutes at about 37 °C.

73. The method of claim 68, wherein said poorly crystalline apatitic calcium phosphate has x-ray diffraction substantially as shown in Figure [18] 7.

74. The method of claim 68, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

75. The method of claim 68, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate is characterized in that, when placed in a rat intramuscular site, resorption of at least 1 g of the material is at least 80% resorbed within one year.

76. The method of claim 68, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate is characterized in that, when placed in a rat intramuscular site, resorption of at least 1 g of the material is at least 80% resorbed within one month.

77. The method of claim 68 or 69, wherein the implant site comprises a tooth socket.

78. The method of claim 68 or 69, wherein the implant site comprises a non-union bone.

79. The method of claim 68 or 69, wherein the implant site comprises a bone prosthesis.

80. The method of claim 68 or 69, wherein the implant site comprises an osteoporotic bone.

81. The method of claim 68 or 69, wherein the implant site comprises an intervertebral space.

82. The method of claim 68 or 69, wherein the implant site comprises a alveolar ridge.

83. The method of claim 68 or 69, wherein the implant site comprises a bone fracture.

84. A method of preparing a ceramic implant, comprising:

mixing in any order,

(a) [a reactive] an amorphous calcium phosphate,

(b) a second calcium phosphate, the second calcium phosphate and the [reactive] amorphous calcium phosphate in a proportion to form an apatitic calcium phosphate, and

(c) a physiological liquid, said liquid in the amount to provide a paste or putty; and

introducing the paste or putty into an implant site, whereby the paste or putty hardens, said hardening associated with an endothermic reaction.

85. [The method of claim 84,] A method of preparing a ceramic implant, comprising:

mixing in any order,

(a) [a reactive] an amorphous calcium phosphate,

(b) a second calcium phosphate, the second calcium phosphate and the [reactive] amorphous calcium phosphate in a proportion to form an apatitic calcium phosphate, and

(c) a physiological liquid, said liquid in the amount to provide a paste or putty; and

introducing the paste or putty into an implant site wherein the [reaction is carried out at no greater than about 37 °C] paste is injectable for a time greater than about 10 minutes at about 22 °C, hardens within about 10 to 60 minutes at about 37 °C.

86. The method of claim 84, wherein the fluid selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

87. The method of claim 84, wherein the paste or putty is injected into the implant site.

88. A method for embedding a prosthetic device into a bone, comprising:

introducing an implant device at a bone site;

applying a strongly resorbable, poorly crystalline apatitic calcium phosphate in the form of a powder, paste or putty to the implant device, whereby the poorly crystalline apatitic calcium phosphate is resorbed at the implant site and replaced thereby with new bone growth.

89. A method for treating a bone defect comprising:

identifying a bone site suitable for receiving an implant;

introducing pressed powder compact at the bone site, said pressed powder compact having approximately the shape required for repair of the bone defect and comprising an amorphous calcium phosphate and a promoter for promoting the conversion of the amorphous calcium phosphate into a strongly resorbable, poorly crystalline apatitic calcium phosphate, whereby the pressed powder compact is converted in vivo into the strongly resorbable poorly crystalline apatitic calcium phosphate.

100. A reactive amorphous calcium phosphate material having at least 90% percent amorphous character and characterized in that, when prepared 1:1 as a mixture with dicalcium diphosphate in water, the mixture remains injectable and formable for a time greater than about 60 minutes at about 22 °C and hardens at about 37 °C within about 10 to about 60 minutes, said material suitable for use in a bone substitute material.

101. The amorphous calcium phosphate material of claim 100, having a specific surface area of greater than about 100 sq. m/g.

102. The amorphous calcium phosphate material of claim 100, wherein the specific surface area is about 120 sq. m/ g.

103. The amorphous calcium phosphate of claim 100, further characterized as having an average pore size of 130Å.

104. The amorphous calcium phosphate of claim 100, wherein the mixture hardens within about 60 minutes at about 37 °C.

Simkiss does not teach a poorly crystalline apatitic hydroxyapatite having been formed in a process involving an endothermic reaction. Nor is there any teaching or disclosure of strongly bioresorbable properties. For these reasons, it is submitted that Tung, in view of Simkiss does not render the claims obvious and it is submitted that the claims possess an inventive step.

Conclusion

For the forgoing reasons, it is submitted that claims possess both novelty and inventive step. A favorable International Examination Report is respectfully requested. Please charge any additional fees or credit any overpayment to our Deposit Account No. 03-1721.

Respectfully Submitted,

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1. A self-hardening bioceramic composition, comprising:

a calcium phosphate and an aqueous-based liquid in an amount sufficient to hydrate the calcium phosphate to form a paste or putty, wherein the said paste or putty hardens and the hardening is associated with an endothermic reaction.

2. The self-hardening bioceramic composition of claim 1, wherein the said paste or putty remains injectable or formable for a time greater than about 30 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

3. The composition of claim 2, wherein hardening occurs in more than 30 minutes.

4. The composition of claim 1, wherein the aqueous-based fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

5. The composition of claim 1 or 2, wherein the calcium phosphate comprises an amorphous calcium phosphate.

6. The composition of claim 1 or 2, wherein the calcium phosphate comprises a nanocrystalline calcium phosphate.

7. The composition of claim 1 or 2, wherein the hardening of the hydrated precursor is further associated with the conversion of the calcium phosphate into a poorly crystalline apatitic calcium phosphate.

8. The composition of claim 7, further comprising a promoter, said promoter further capable of promoting the conversion of calcium phosphate into a poorly crystalline apatitic calcium phosphate.

9. The composition of claim 8, wherein the promoter is selected from

the group consisting of passive promoters and participant promoters.

10. The composition of claim 9, wherein the promoter is a passive promoter selected from the group consisting of metals, metal oxides, ceramics, silicates, sugars, salts, and polymeric particulates

11. The composition of claim 9, wherein the promoter is a passive promoter and said passive promoter is present in the range of about 1:1 to about 5:1 calcium phosphate:promoter.

12. The composition of claim 9, wherein the promoter is a passive promoter selected from the group consisting of SiO_2, mica, Al_2O_3, poly(L-lactide) (PLLA), polyglycolide (PGA), and poly(lactide-co-glycolide (PLGA) copolymers.

13. The composition of claim 9, wherein the promoter is a participant promoter selected from the group consisting of calcium and phosphorus sources.

14. The composition of claim 9, wherein the promoter is a participant promoter selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline hydroxyapatite, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

15. The composition of claim 9, wherein the promoter comprises DCPD.

16. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size less than about 200μm.

17. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size of less than about 95μm.

18. The composition of claim 9, wherein the promoter comprises DCPD having an average grain size of about 35 - 45μm and a grain size maximum of less than about 110 μm.

19. The composition of claim 1 or 2, further characterized in that hardening occurs in more than 24 hours at about 4 °C.

20. The composition of claim 1, wherein the amount of liquid is in the range of about 0.5 to about 2.0 mL liquid/g calcium phosphate.

21. A bioceramic composition, comprising:

a poorly crystalline calcium phosphate prepared by,

promoting the hardening of a hydrated precursor comprising an amorphous calcium phosphate and an aqueous-based liquid in an amount sufficient to hydrate the amorphous calcium phosphate to form a paste or putty,

whereby hardening is associated with an endothermic reaction and the conversion of the amorphous calcium phosphate into the poorly crystalline calcium phosphate.

22. A bioceramic composition, comprising:

a strongly bioresorbable, poorly crystalline apatitic calcium phosphate.

23. The composition of claim 21 or 22, wherein said poorly crystalline apatitic calcium phosphate has an X-ray diffraction substantially as shown in Figure 7.

24. The composition of claim 22, wherein the strongly resorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

25. The composition of claim 22, wherein the X-ray diffractions pattern is characterized by an absence of peaks associated with the 210 Miller Index.

26. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one year when 1 g of the composite is placed in a rat intramuscular site.

27. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within nine months when 1 g of the composite is placed in a rat intramuscular site.

28. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within six months when 1 g of the composite is placed in a rat intramuscular site.

29. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within three months when 1 g of the composite is placed in a rat intramuscular site.

30. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one month when 1 g of the composite is placed in a rat intramuscular site.

31. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is formulated so that when implanted *in vivo* in a bone site, new bone substantially replaces the composite within six months.

32. The composition of claim 22, wherein the poorly crystalline apatitic calcium phosphate is formulated so that when implanted *in vivo* in a bone site, new bone substantially replaces the composite within six weeks.

33. The composition of claim 22, wherein powders of the poorly crystalline apatitic calcium phosphate are pressed into a powder compact of a predetermined shape.

34. A method of preparing a bioceramic composition, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a promoter, and

(c) an aqueous-based liquid in an amount sufficient to form a paste or putty, whereby the paste or putty is converted into a poorly crystalline apatitic calcium phosphate and said conversion is associated with hardening of the paste in an endothermic reaction.

35. The method of claim 34, wherein the promoter is selected from the group consisting of SiO_2, Al_2O_3, sand, mica and glass.

36. The method of claim 34, wherein the promoter is a calcium or a phosphorus source.

37. The method of claim 36, wherein the calcium or phosphate source is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline hydroxyapatite, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

38. The method of claim 34, wherein the paste or putty is injectable and formable for a time greater than about 10 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

39. The method of claim 34, wherein the fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution,

saline solution, serum and tissue culture medium.

40. A method of preparing a bioceramic composition, comprising:

mixing powders of an amorphous calcium phosphate and a promoter; and

pressing the powders to form a powder compact of a predetermined shape.

41. The method of claim 40, further comprising hydrating the powder compact to promote conversion of the mixed powders to a poorly crystalline apatitic calcium phosphate.

42. The method of claim 40, wherein the fluid is selected from the group consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

43. A bioceramic composition, comprising:

powders of an amorphous calcium phosphate and a promoter compressed to form a powder compact of a predetermined shape.

44. A composite material comprising:

(a) a poorly crystalline apatitic calcium phosphate made by the process comprising:

providing an amorphous calcium phosphate in the presence of a sufficient quantity of water to produce a paste; and

promoting the hardening of the paste, wherein said hardening is associated with an endothermic reaction and the conversion of the amorphous calcium phosphate to a poorly crystalline apatitic calcium phosphate; and

(b) a supplemental material in intimate contact with the poorly crystalline apatitic calcium phosphate, said supplemental material present in an amount effective to impart a selected characteristic to the composite.

45. A composite material comprising:

(a) a poorly crystalline apatitic calcium phosphate made by the process

comprising:

providing an amorphous calcium phosphate in the presence of a sufficient quantity of water to produce a paste; and

promoting the hardening of the paste, characterized in that, said paste, when prepared from a reaction of amorphous calcium phosphate and a second phosphate in a fluid, is injectable or formable for a time greater than about 10 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C; and

(b) a supplemental material in intimate contact with the poorly crystalline apatitic calcium phosphate, said supplemental material present in an amount effective to impart a selected characteristic to the composite..

46. A composite material, comprising:

a strongly bioresorbable, poorly crystalline apatitic calcium phosphate in intimate contact with a biocompatible supplemental material, said supplemental material present in an amount effective to impart a selected characteristic to the composite.

47. The composite of claim 46, wherein said poorly crystalline apatitic calcium phosphate has x-ray diffraction substantially as shown in Figure [18] 7.

48. The composite of claim 46, wherein the strongly resorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

49. The composite of claim 46, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one year when 1 g of the composite is placed in a rat intramuscular site

50. The composite of claim 46, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within nine months when 1 g of

the composite is placed in a rat intramuscular site

51. The composite of claim 46, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within six months when 1 g of the composite is placed in a rat intramuscular site

52. The composite of claim 46, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within three months when 1 g of the composite is placed in a rat intramuscular site

53. The composite of claim 46, wherein the poorly crystalline apatitic calcium phosphate is characterized in that at least about 80% of the poorly crystalline apatitic calcium phosphate is resorbed within one month when 1 g of the composite is placed in a rat intramuscular site

54. The composite of claim 46, wherein the supplementary material is bioresorbable.

55. The composite of claim 54, wherein the resorbable supplementary material is selected from the group consisting of collagen, demineralized bone matrix, derivativized hyaluronic acid, polyanhydrides, polyorthoesters, polyglycolic acid, alginate, polylactic acid, and copolymers thereof, polyesters of α-hydroxycarboxylic acids, poly(L-lactide) (PLLA), poly(D,L-lactide) (PDLLA), polyglycolide (PGA), poly(lactide-co-glycolide (PLGA), poly(D,L-lactide-co-trimethylene carbonate), and polyhydroxybutyrate (PHB), polyanhydrides, poly(anhydride-co-imide) and co-polymers thereof, and bioactive glass compositions.

56. The composite of claim 46, wherein supplementary material is non-bioresorbable.

57. The composite of claim 56, wherein the non-bioresorbable supplementary material is selected from the group consisting of dextrans, polyethylene, polymethylmethacrylate (PMMA), carbon fibers, polyvinyl alcohol (PVA), poly(ethylene terephthalate)polyamide, bioglasses, calcium sulfate and calcium phosphates

58. The composite of claim 46, wherein the supplementary material is a lubricant.

59. The composite of claim 58, wherein the lubricant is selected from the group consisting of silicone oil, polymer waxes, lipids, surfactants and fatty acids.

60. The composite material of claim 58, wherein the lubricant in present in an amount in the range of about 0.1-30 wt%.

61. The composite material of claim 46, wherein the supplementary material comprises a radiographic material.

62. The composite of claim 46, wherein the supplementary material is in the form selected from the group consisting of foam, sponge, mesh, particles, fibers, gels and filaments.

63. The composite material of claim 46, wherein the supplementary material is in the form of a fiber and the fiber is present in an amount in the range of about 0.01-50 wt%.

64. A method of preparing a ceramic composite material, comprising:
mixing in any order,
(a) an amorphous calcium phosphate,
(b) a promoter, and
(c) a supplementary material, the supplementary material present in an

amount effective to impart a selected characteristic to the composite; and

initiating conversion of the amorphous calcium phosphate into a poorly crystalline apatitic calcium phosphate, said conversion is associated with an endothermic reaction.

65. The method of claim 64, wherein the promoter is selected from the group consisting of Al_2O_3, sand, mica and glass.

66. The method of claim 64, wherein the promoter is a calcium or a phosphorus source.

67. The method of claim 66, wherein the promoter is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, crystalline HA, PCA calcium phosphate, calcium pyrophosphate, monetite, octacalcium phosphate, CaO, $CaCO_3$, calcium acetate, and H_3PO_4, and ACP.

68. A method of preparing a ceramic composite material, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a promoter, and

(c) a supplementary material, the supplementary material present in an amount effective to impart a selected characteristic to the composite; and

initiating conversion of the amorphous calcium phosphate into a poorly crystalline apatitic calcium phosphate, wherein the reaction mixture is injectable or formable for a time greater than about 10 minutes at about 22 °C, and hardens within about 10 to 60 minutes at about 37 °C.

69. The method of claim 64, wherein the reaction to form a poorly crystalline apatitic calcium phosphate is initiated before addition of the supplementary material.

preparing a composite comprising a fully resorbable, poorly crystalline apatitic calcium phosphate in intimate contact with a non-resorbable or weakly resorbable supplementary material;

introducing the composite to a bone site, whereby the fully resorbable poorly crystalline apatitic calcium phosphate is resorbed and ossified and the non-resorbable supplementary material remains at the bone site.

81. A method for treating a bone defect, comprising:

identifying a bone site suitable for receiving an implant; and

introducing a strongly resorbable, poorly crystalline apatitic calcium phosphate at the implant site, whereby bone is formed at the implant site.

82. A method for treating a bone defect, comprising:

identifying a bone site suitable for receiving an implant; and

introducing a hydrated precursor to a strongly resorbable, poorly crystalline apatitic calcium phosphate at the implant site, whereby the hydrated precursor is converted *in vivo* to a poorly crystalline apatitic calcium phosphate and whereby bone is formed at the implant site.

83. The method of claim 80, wherein the poorly crystalline apatitic calcium phosphate is introduced in the form selected from the group consisting of paste, putty and preshaped object.

84. The method of claim 81, wherein the poorly crystalline apatitic calcium phosphate is introduced in the form selected from the group consisting of paste, putty and preshaped object.

85. The method of claim 82, wherein the hydrated precursor is introduced in the form selected from the group consisting of paste and putty.

86. The method of claim 83, 84 or 85, characterized in that, said paste is injectable for a time greater than about 10 minutes at about 22 °C, hardens

within about 10 to 60 minutes at about 37 °C.

87. The method of claim 81, wherein said poorly crystalline apatitic calcium phosphate has x-ray diffraction substantially as shown in Figure 7.

88. The method of claim 81, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32° and 33°.

89. The method of claim 81, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate is characterized in that, when placed in a rat intramuscular site, resorption of at least 1 g of the material is at least 80% resorbed within one year.

90. The method of claim 81, wherein the strongly bioresorbable, poorly crystalline apatitic calcium phosphate is characterized in that, when placed in a rat intramuscular site, resorption of at least 1 g of the material is at least 80% resorbed within one month.

91. The method of claim 81 or 82, wherein the implant site comprises a tooth socket.

92. The method of claim 81 or 82, wherein the implant site comprises a non-union bone.

93. The method of claim 81 or 82, wherein the implant site comprises a bone prosthesis.

94. The method of claim 81 or 82, wherein the implant site comprises an osteoporotic bone.

95. The method of claim 81 or 82, wherein the implant site comprises

an intervertebral space.

96. The method of claim 81 or 82, wherein the implant site comprises a alveolar ridge.

97. The method of claim 81 or 82, wherein the implant site comprises a bone fracture.

98. A method of preparing a ceramic implant, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a second calcium phosphate, the second calcium phosphate and the amorphous calcium phosphate in a proportion to form an apatitic calcium phosphate, and

(c) a physiological liquid, said liquid in the amount to provide a paste or putty; and

introducing the paste or putty into an implant site, whereby the paste or putty hardens, said hardening associated with an endothermic reaction.

99. A method of preparing a ceramic implant, comprising:

mixing in any order,

(a) an amorphous calcium phosphate,

(b) a second calcium phosphate, the second calcium phosphate and the amorphous calcium phosphate in a proportion to form an apatitic calcium phosphate, and

(c) a physiological liquid, said liquid in the amount to provide a paste or putty; and

introducing the paste or putty into an implant site wherein the paste is injectable for a time greater than about 10 minutes at about 22 °C, hardens within about 10 to 60 minutes at about 37 °C.

100. The method of claim 98, wherein the fluid selected from the group

consisting of water, a physiologically acceptable pH-buffered solution, saline solution, serum and tissue culture medium.

101. The method of claim 98, wherein the paste or putty is injected into the implant site.

102. A method for embedding a prosthetic device into a bone, comprising:

introducing an implant device at a bone site;

applying a strongly resorbable, poorly crystalline apatitic calcium phosphate in the form of a powder, paste or putty to the implant device, whereby the poorly crystalline apatitic calcium phosphate is resorbed at the implant site and replaced thereby with new bone growth.

103. A method for treating a bone defect comprising:

identifying a bone site suitable for receiving an implant;

introducing pressed powder compact at the bone site, said pressed powder compact having approximately the shape required for repair of the bone defect and comprising an amorphous calcium phosphate and a promoter for promoting the conversion of the amorphous calcium phosphate into a strongly resorbable, poorly crystalline apatitic calcium phosphate, whereby the pressed powder compact is converted in vivo into the strongly resorbable poorly crystalline apatitic calcium phosphate.

104. A reactive amorphous calcium phosphate material having at least 90% percent amorphous character and characterized in that, when prepared 1:1 as a mixture with dicalcium diphosphate in water, the mixture remains injectable and formable for a time greater than about 60 minutes at about 22 °C and hardens at about 37 °C within about 10 to about 60 minutes, said material suitable for use in a bone substitute material.

105. The amorphous calcium phosphate material of claim 104, having a

specific surface area of greater than about 100 sq. m. g.

106. The amorphous calcium phosphate material of claim 104, wherein the specific surface area is about 120 sq. m g.

107. The amorphous calcium phosphate of claim 104, further characterized as having an average pore size of 130Å.

108. The amorphous calcium phosphate of claim 104, wherein the mixture hardens within about 60 minutes at about 37 °C.

109. The amorphous calcium phosphate of claim 104, wherein the calcium to phosphate ratio is about 1.55 to 1.65.

110. The amorphous calcium phosphate of claim 104, wherein said reactivity is obtained by introduction of chemical vacancies into the material.